Case Report from The New York–New Jersey Intercity Infectious Disease Rounds
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Septic Shock in a 31-Year-Old Male with a Superficial Bladder Tumor

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A 32-year-old Hispanic male, with a 5-year history of transitional cell carcinoma in situ of the bladder, was admitted with rigors, fever of 40°C, scleral icterus, and abdominal pain. Three days prior to admission he had received his first intravesical irrigation with bacille Calmette-Guérin (BCG) vaccine. The bladder irrigation proceeded uneventfully. However, at the time of his first voiding, approximately 2 hours after BCG instillation, chills, headache, and dizziness were noted. Symptoms persisted and worsened, and fever was noted. The patient presented to the emergency room for evaluation 72 hours after bladder irrigation and was admitted to hospital.

The patient was born in the United States and had no history of foreign travel. He works in an office setting for an international auction house but does not handle auctioned items. He lives with his girlfriend who is in good health. His tuberculin status and human immunodeficiency virus (HIV) status were unknown on admission, but both were subsequently shown to be negative. His only previous hospitalizations were for diagnosis of the transitional cell carcinoma in situ of the bladder, which was diagnosed during his first evaluation of hematuria, and for ambulatory cystoscopic fulgurations of the bladder over the past 5 years; the latest, more than 6 months prior to BCG immunotherapy. He had no other known underlying medical problems and took no chronic medications.

On admission to hospital, the patient's physical examination was significant for tachycardia, drenching sweats, blood pressure of 90/60 mmHg, a clear auscultatory chest examination, a hemic I-VI systolic ejection murmur, a benign abdominal examination, and a normal neurologic examination. A hemogram revealed a white blood cell count (WBC) of 6000, a hematocrit of 45%, and a platelet count of 155,000. The WBC comprised 72% neutrophils, 10% lymphocytes, 3% monocytes, and 15% bands. Blood chemistry values were normal except for a mildly elevated lactate dehydrogenase (LDH) of 279 IU/L (normal range, 100–225 IU/L), an aspartate aminotransferase (AST) of 161 IU/L (normal range, 7–40 IU/L), and a serum alanine aminotransferase (ALT) of 165 IU/L (normal range, 10–60 IU/L). Total bilirubin was 3.0 mg/dL (normal range, 0.2–1.2 mg/dL), and gamma-glutamyl transpeptidase (GGTP) was 165 IU/L (normal range, 7–64 IU/L). A urine analysis revealed yellow, clear urine with a pH of 7, with no white or red blood cells. After appropriate cultures, antibiotic therapy was begun with cefazolin, and intravenous fluids were administered. A working diagnosis of acute hepatitis or sepsis was entertained.

Over the next 48 hours the patient's condition deteriorated, and he required transfer to the intensive care unit (ICU) for therapy of apparent septic shock. An initial chest radiograph was negative, but a subsequent gallium scan was consistent with diffuse pneumonitis (Figure 1). Evaluations for hepatitis A, B, and C were all negative. Fever and hepatitis persisted. All routine cultures remained negative. Chest radiograph obtained during the patient's confinement to the ICU revealed bilateral lower lobe infiltrates (Figure 2).

HOSPITAL COURSE

On admission, the differential diagnosis included sepsis, pneumonia, acute hepatitis, and urosepsis as a cause for

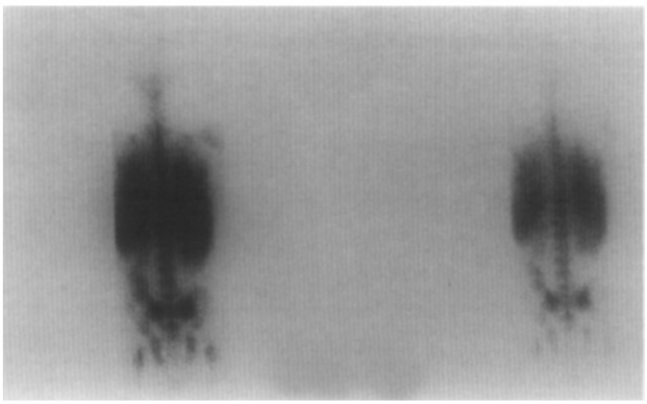

Figure 1. Anterior and posterior gallium scans showing a diffuse uptake in all lung fields and increased uptake in the liver.

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Figure 2. Chest radiograph taken during stay in the ICU showing bilateral lower lobe pneumonia.

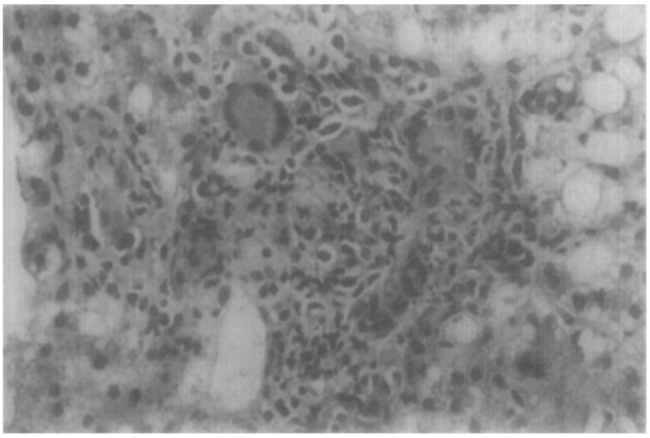

Figure 4. High-power photomicrograph of liver granuloma (H&E) showing typical multinucleated giant cells.

multiorgan failure. However, initial and subsequent urine analyses were normal, and all routine cultures of the blood and urine were sterile. Initially, complications from the BCG therapy were thought to be unlikely, because urine analyses were normal, systemic signs and symptoms predominated, this was the first instillation of the BCG, there was no evidence of previous erosive cystitis, and the procedure itself was uncomplicated. Multiple organ system involvement initially pointed toward sepsis from more common gram-negative pathogens that would be associated with any urologic procedure. However, all routine cultures were being reported negative and multiple organ system failure and diffuse intravascular coagulopathy ensued. Treatment required ventilatory support for pulmonary insufficiency, hemodialysis for acute renal failure, and multiple transfusions of blood products for treatment of disseminated intravascular coagulation and concurrent upper gastrointestinal bleeding. A clinical diagnosis of BCG sepsis (disseminated BCG infection with multiple system failure: pulmonary, hepatic, renal) was assumed, and treatment was initiated with isoniazid and rifampin. Ethambutol was added subsequently when oral feeding was instituted.

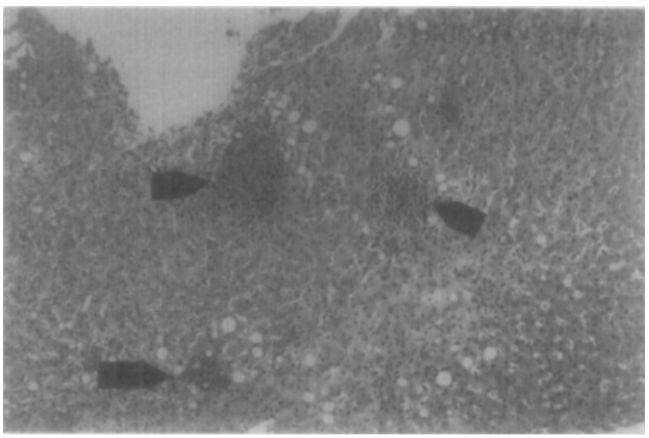

Figure 3. Low-power photomicrograph of liver biopsy (H&E) on day 21 of therapy showing multiple granulomas in the liver parenchyma (arrows).

Acute renal failure with the blood urea nitrogen rising to 112 mg/dL (normal range, 10–26 mg/dL), and the creatinine to 12 mg/dL (normal range, 0.5–1.4 mg/dL) required 5 days of hemodialysis. An acute bleeding duodenal ulcer and diffuse gastritis were diagnosed by endoscopy. Antibiotic treatment during this time was expanded to include vancomycin and imipenem. The patient was supported with transfusions of fresh frozen plasma (29 units), packed red blood cells (28 units), platelets (8 units), and cryoprecipitate (12 units). Severe metabolic acidosis, with the serum CO_2 dropping to 2.9 mEq/L (normal range, 24–32 mEq/L) required correction with intravenous bicarbonate. A liver biopsy, performed on day 21 after starting anti-mycobacteria therapy, revealed a granulomatous hepatitis with no acid-fast bacilli seen (Figures 3 and 4). Chest radiographs remained consistent with diffuse pneumonitis. Over the next 7 days the patient slowly improved; renal, hepatic, and pulmonary functions normalized, and he was discharged 33 days after hospital admission.

ETIOLOGIC IDENTIFICATION

Seven weeks after admission, cultures of blood but not of urine were reported to be growing an acid-fast bacillus (AFB). The blood isolate and an isolate from a BCG vaccine companion vial were sent to the Centers for Disease Control and Prevention (CDC) for identification. Analysis by high-performance liquid chromatography (HPLC) revealed that both isolates had the identical patterns of BCG strains that identify the isolates as distinct from virulent *Mycobacterium tuberculosis* or *Mycobacterium bovis* (Figure 5).[1] The HPLC clearly identified the

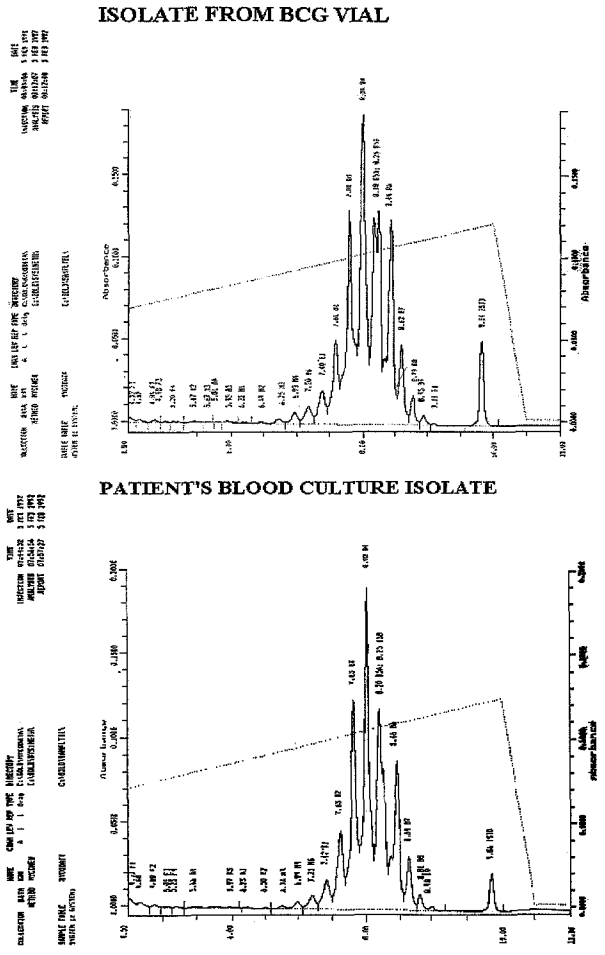

Figure 5. High-performance liquid chromatography showing identical patterns for the companion vial BCG isolate (*A*) and the blood BCG isolate (*B*).

blood isolate as identical to the isolate used for the initial bladder irrigation in this patient. Although the presumed portal of entry for the BCG would be the bladder, urine analyses were normal and both routine and AFB cultures of the urine were negative.

Iseman, at the National Jewish Center in Denver, identified the strain used for immunotherapy (companion vial) and the organism recovered from the patient's blood culture both as *M. bovis* and showed that the two organisms had identical anti-mycobacterial sensitivity profiles (i.e., sensitive to isoniazid, rifampin, ethambutol, streptomycin, capreomycin, kanamycin, amikacin, and cycloserine) at all concentrations tested. Both isolates demonstrated a 2% resistance to *p*-aminosalicylic acid (PAS) when tested at the 8.0 μg concentration.

Because of the question of an abnormal host response to the initial bladder irrigation, immunologic evaluation was performed. The patient had, and continues to have multiple normal CD4 and CD8 cell studies. His purified protein derivative (PPD) converted to positive for the first year and then reverted to negative (a usual finding after BCG vaccination). A 5-year follow-up period has elapsed, during which time he has remained well, and remains HIV-1 negative. Follow-up cystoscopies and biopsies have remained negative and no further BCG immunotherapy has been required.

DISCUSSION

Bacille Calmette-Guérin immunotherapy of carcinoma in situ of the bladder was first reported by Morales et al in 1976,[2] and since then thousands of patient treatment courses have confirmed that BCG immunotherapy is effective and relatively safe. Serious adverse reactions to BCG immunotherapy rarely are reported; the treatment is usually well tolerated.[3] Most reported complications have been minor and self-limited; systemic complications occur only occasionally.[4] Localized reactions, such as granulomatous tuberculous epididymo-orchitis,[5] granulomatous prostatitis,[6] and BCG pyelonephritis,[7] have been reported. The systemic complications reported have included granulomatous hepatitis,[8] the "BCGitis" syndrome,[9] miliary tuberculosis,[10,11] and systemic dissemination.[12] Rarely, fatal outcomes have been reported.[13]

The patient described in this case report clearly demonstrated a rare complication of BCG immunotherapy. His disease pattern included mycobacteremia, pneumonia, hepatitis, diffuse intravascular coagulation, and shock. He is a young man in generally good health, and this was his first intravesical instillation of BCG; therefore, he was not presensitized to BCG, as would be expected after multiple treatments. He had no immunologic deficiencies, and his rapid deterioration was remarkable. Once the diagnosis was suspected, treatment included three antituberculous drugs, because of his extremely poor clinical status. The literature suggests that isoniazid therapy alone would have been adequate. Although the sensitivities of both the BCG strain and the blood culture isolate from the patient confirmed that in 1991 this would have been adequate therapy, this may not be true in the future, owing to developing drug resistance.

The use of high-performance liquid chromatography and simultaneous cultures of the blood isolate and the BCG companion vial isolate in this case confirmed that the organism causing the sepsis was the organism used for BCG immunotherapy. The "BCGitis" syndrome seen in this case was not an allergic reaction to the mycobacterium, but an invasive mycobacteremia.

This patient's follow-up has now extended over 5 years, and repeated cystoscopic evaluations have failed to reveal tumor recurrence. He has remained healthy and fully functional. His PPD and HIV-1 antibody remain negative. It would appear that a single episode of BCG

immunotherapy, one that was associated with an exuberant systemic reaction and major morbidity, was successful in preventing tumor recurrence over the past 5 years.

This case illustrates a serious potential complication of BCG immunotherapy. Patients developing complications temporally related to BCG instillation should, after appropriate cultures, be treated with isoniazid with or without additional drugs while the diagnosis is being clarified. Surveillance for isoniazid resistance among BCG isolates may be required in the future.

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